A request for a two-month extension of time to respond is included herewith along with the required fee. This two-month extension will bring the due date to June 4, 1999, which is within the six-month statutory period. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Arnold, White & Durkee Deposit Account No. 01-2508/UTXC:504/STA.

Reconsideration of the application is respectfully requested.

I. AMENDMENT

In the Claims:

Please amend the claims as follows:

SUB E1

1. (Four Times Amended) A composition comprising a first polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions and a neutral lipid associated with said first polynucleotide, to form a Bcl-2 polynucleotide/neutral lipid association, wherein said first polynucleotide comprises at least 8 nucleotides of the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

SUB E2

9. (Thrice Amended) A composition comprising an expression construct that encodes a first polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions, wherein said construct is under the control of a promoter that is active in eukaryotic cells and associated with a neutral lipid, wherein said first polynucleotide comprises at least 8 nucleotides of the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

SUB E3

31. (Amended) A neutral lipid oligonucleotide association comprising a neutral lipid associated with an oligonucleotide of from about 8 to about 50 bases and complementary to at

SUB E3 COO:X.

D3 Cont

least 8 bases of the translation initiation site of Bcl-2 mRNA, wherein said translation initiation site comprises the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

SUB E4

52. (Amended) A composition comprising a first polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions and a primary phosphatide associated with said first polynucleotide, wherein said primary phosphatide is a neutral lipid, and wherein said first polynucleotide comprises at least 8 nucleotides of the sequence CAGCGTGCGCCATCCTTC (SEQ ID NO:1).

D4

Please cancel claims 42 and 51 without prejudice or disclaimer.

Please add the following claim:

D5

--56. The composition of claim 1, wherein said at least 8 nucleotides are consecutive nucleotides.--

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1, 9, 31 and 52 have been amended. Claims 42 and 51 have been cancelled without prejudice or disclaimer. Claim 56 has been added. Claims 1-41, 43-50 and 52-56 are therefore pending.

For the convenience of the Examiner, a copy of the pending claims is attached hereto as **Exhibit A**.

B. Amendments to the Claims

Applicants have amended claims 1, 9, 31 and 52 to more distinctly claim the invention as a polynucleotide that comprises at least eight nucleotides of SEQ ID NO:1, in response to the written description rejection under 35 U.S.C. § 112, first paragraph. Support for these revisions

can be found at page 4, lines 15-20; page 5, line 27 to page 6, line 6; page 6, lines 17-23; page 10, line 25 to page 11, line 13; page 12, lines 1-12; page 13, lines 1-25; page 33, lines 5-11; and throughout the specification as filed as a whole.

New claim 56 has been added for the Examiner's review. Any additional fees necessitated by the presently added claim should be deducted from Applicants' representative's Deposit Account No. 01-2508/UTXC:504/STA.

To progress the case to allowance, claims 42 and 51 have been cancelled without prejudice or disclaimer.

Claim 56 has been added to describe embodiments of the invention wherein the eight nucleotides of the oligonucleotide are consecutive. Support for this claim may be found throughout the specification and claims as filed. Particular written support is found at least at page 6, lines 17-23; page 13, lines 1-25; page 10, line 25 to page 11, line 13; page 12, lines 1-12; page 13, lines 1-25; and throughout the specification as filed as a whole.

In light of the foregoing information, it will be understood that no new matter is included within any of the amended or added claims.

C. The Rejection of Claims 1-3, 5-9, 31, 33-42 and 47-55 Under 35 U.S.C. § 112, First Paragraph Is Overcome

The Action has rejected claims 1-3, 5-9, 31, 33-42 and 47-55 under 35 U.S.C. § 112, first paragraph, as not meeting the "written description" requirement.

Applicants respectfully traverse. The presently claimed invention meets the written description requirement of 35 U.S.C. § 112, First Paragraph.

The Action argues that the "specification suggests regions within the BCL-2 gene which could be targeted by an antisense oligonucleotide." The specification provides written description

for polynucleotides that hybridize to specific regions in the Bcl-2 gene, *i.e.* the translation initiation site of the BCL-2 gene, and describes examples of polynucleotides that hybridize to this region, and those that do not, at page 33, lines 5-11:

> Nuclease-resistant p-ethoxy oligonucleotides, non-ionic phosphodiester analogs, were purchased from Oligo Therapeutics (Willsonville, OR). An oligonucleotide specific for the translation initiation site of human Bcl-2 mRNA: $^{5'}$CAGCGTGCGCCATCCTTC$^{3'}$ (SEQ ID NO:1) was used as antisense oligonucleotide. Two different control oligonucleotides were used: $^{5'}$ACGGTCCGCCACTCCTTCCC$^{3'}$ (SEQ ID NO:2) (scrambled version of Bcl-2 antisense oligonucleotide) and the random sequence $^{5'}$CTGAAGGGCTTCTTCC$^{3'}$(SEQ ID NO:3).

The Action argues that it is "unknown what properties, structural or otherwise, said composition must possess for it to decrease the level of BCL-2 in a cell." The specification fully describes the structural properties of a composition that can decrease the Bcl-2 gene's expression in a cell, through the disclosure of the sequence of SEQ ID NO:1 and the effect of an oligonucleotide comprising this sequence on the Bcl-2 gene's expression. The specification provides written description of oligonucleotide sequences that may be derived from this targeted region, at page 10, line 25 to page 21, line 11. In particular, the specification provides written description for oligonucleotides that are complementary to a portion of the Bcl-2 gene, at page 10, line 25 to page 11, line 13:

> The term "antisense" is intended to refer to polynucleotide molecules complementary to a portion of a Bcl-2 RNA, or the DNA's corresponding thereto. "Complementary" polynucleotides are those which are capable of base-pairing according to the standard Watson-Crick complementarity rules. That is, the larger purines will base pair with the smaller pyrimidines to form combinations of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. Inclusion of less common bases such as inosine, 5-methylcytosine, 6-methyladenine, hypoxanthine and others in hybridizing sequences does not interfere with pairing.
>
> Targeting double-stranded (ds) DNA with polynucleotides leads to triple-helix formation; targeting RNA will lead to double-helix formation. Antisense

> polynucleotides, when introduced into a target cell, specifically bind to their target polynucleotide and interfere with transcription, RNA processing, transport, translation and/or stability. Antisense RNA constructs, or DNA encoding such antisense RNA's, may be employed to inhibit gene transcription or translation or both within a host cell, either *in vitro* or *in vivo*, such as within a host animal, including a human subject.

The specification also provides written description for the lengths of oligonucleotides of the present invention that may be used, at page 13, lines 12-18.

> Although shorter oligomers (8-20) are easier to make and increase *in vivo* accessibility, numerous other factors are involved in determining the specificity of base-pairing. For example, both binding affinity and sequence specificity of an oligonucleotide to its complementary target increase with increasing length. It is contemplated that oligonucleotides of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45 or 50 base pairs or larger may be used.

The specification also provides written description for oligonucleotides that are not completely complementary, at page 12, lines 1-12:

> As used herein, the terms "complementary" or "antisense" mean polynucleotides that are substantially complementary over their entire length and have very few base mismatches. For example, **sequences of fifteen bases in length may be termed complementary when they have a complementary nucleotide for thirteen or fourteen positions out of fifteen.** Naturally, sequences which are "completely complementary" will be sequences which are entirely complementary throughout their entire length and have no base mismatches.
>
> Other sequences with lower degrees of homology also are contemplated. For example, an antisense construct which has limited regions of high homology, but also contains a non-homologous region (*e.g.*, a ribozyme) could be designed. These molecules, **though having less than 50% homology, would bind to target sequences under appropriate conditions.** (Emphasis added)

Thus, the specification provides ample written description for the structural characteristics and properties of the claimed invention through the description of SEQ ID NO:1, complementary oligonucleotides that bind the Bcl-2 gene, the size ranges of various oligonucleotides may that be made, an example of an oligonucleotide that is not completely complementary but still may be used, a description of a completely complementary

oligonucleotide (SEQ ID NO:1), and a description of two contrasting oligonucleotides of similar size not designed to be complementary to the Bcl-2 gene that do not effectively inhibit the Bcl-2 gene's expression (SEQ ID NOS, 2 & 3).

Through these descriptions, and those of the specification as a whole, the written description requirement of the presently claimed invention has been met.

Applicants respectfully request that this rejection be withdrawn.

D. The Rejection of Claim 42 Under 35 U.S.C. § 112, First Paragraph Is Overcome

The Action has rejected claim 42 under 35 U.S.C. § 112, first paragraph, as not being enabled.

In response, Applicants hereby cancel claims 42 and 51 without prejudice or disclaimer. This amendment has merely been made to progress the case to allowance.

Applicants respectfully request that this rejection be withdrawn.

E. The Rejection of Claims 1-9, 31-37, 39-41, 48-50 and 52-54 Under 35 U.S.C. § 103(a) Over Evan or Reed or Green *et al.* in view of Tari *et al.* Is Overcome

Claims 1-9, 31-37, 39-41, 48-50 and 52-54 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Evan (WO 93/20200) or Reed (WO 95/08350) or Green *et al.* (U.S. Patent No. 5,583,034) in view of Tari *et al.* (U.S. Patent No. 5,417,978). The Office maintains the rejection made in the previous Action mailed July 7, 1998.

Applicants respectfully traverse. The claimed invention is not obvious relative to these references, either alone or in combination.

The Action has admitted at page 5 that Evan or Reed or Green *et al.* do not teach neutral lipids. The Action bases the motivation to combine these references with Tari *et al.* upon "the teaching of Tari *et al.* that liposomes comprising dioleolphosphatidylcholine impart improved

stability and cellular uptake to the antisense oligonucleotides." Applicants respectfully submits that the Office, in its argument to provide the motivation to combine Tari *et al.* with the other cited references, has incorrectly characterized Tari *et al.* Applicants find that Tari *et al.* does not provide guidance to specifically select a neutral lipid based on these properties. Tari *et al.* teaches that these properties are common to all liposome constructs (*i.e.* "the invention' of the Tari *et al.* reference), at column 2, lines 49-56:

> The advantages of **the invention** include improved stability of the antisense oligonucleotides compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes, and enhanced specific therapeutic effect of the antisense oligonucleotides against CML and other disease conditions in which similar gene rearrangements are observed. (Emphasis added).

The invention of Tari *et al.*, is defined at column 1, line 65 to column 2, line 3:

> The present invention relates to a liposomal methyl phosphonate oligonucleotide composition. The composition comprises (a) a liposome which comprises at least one phospholipid, and (b) an antisense methyl phosphonate oligonucleotide which is entrapped in the liposome.

Applicants submit that the broad teaching of the general advantages of a phospholipid liposome and an antisense methyl phosphonate oligonucleotide, the invention of the Tari *et al.* reference, (column 1, line 66 to column 2, line 3) is not a teaching, suggestion or guidance of the neutral lipid and antisense Bcl-2 oligonucleotide composition of the presently claimed invention (*i.e.* the invention of the rejected claims). The advantages referred to by the Action are disclosed in regards to all liposome constructs described by Tari *et al.*, without a teaching, suggestion or guidance to use either charged or neutral lipids, let alone specifying the lipid dioleolphosphatidylcholine. Thus, this teaching does not provide the necessary guidance to a neutral lipid to combine this reference with the other cited references.

In an attempt to provide the necessary motivation to combine, the Action further argues, at page 6, that only one of the working examples did not utilize dioleoylphosphatidylcholine. This example is shown at column 6, at Table 4 of Tari *et al.*, and demonstrates that the charged lipid dioleoyl (C18:1) phosphatidylserine incorporates the oligonucleotides of Tari *et al.* with an efficiency greater than or equal to (using the margin of error) the compositions comprising neutral lipids. Applicants submit that Tari *et al.* demonstrates that both neutral and charged lipids incorporates oligonucleotides, and that the tested charged lipid does so better than most of the uncharged lipids tested, including dioleoyl (C18:1) phosphatidylcholine.

In an attempt to refute Applicants' previous arguments submitted in the paper dated November 9, 1999 that Tari *et al.* teaches both neutral and charged lipids, the Action further misinterprets the disclosures of Tari *et al.* in its statement at page 8 that "a liposome consisting only of dioleolphosphatidylcholine is used in all the working examples." This statement contradicts the teachings of Tari *et al.* At column 6, Table 4, Tari *et al.* shows a working example where an equal or greater incorporation of oligonucleotides in a charged lipid construct (*i.e.* dioleoyl (C18:1) phosphatidylserine) when compared to dioleoyl (C18:1) phosphatidylcholine ("DOPC") and the majority of uncharged lipid constructs. Applicants submit that this teaching may indicate that charged lipid constructs may be more therapeutically effective than an uncharged liposome construct, as a charged liposome contains as much or more oligonucleotides as uncharged lipids.

The teachings of Tari *et al.*, including the teachings of the benefits of a charged lipid, must be considered as a whole in the evaluation of the obviousness or non-obviousness of the claimed invention, as stated in the MPEP at 2141.02:

> A prior art reference must be considered in its entirely, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)

Applicants submit that there is a difference in the motivation for selecting a type of lipid that has a property of ease of handling in an experimental setting and the motivation for selecting the type of lipid that has a property of high uptake of oligonucleotides. The latter property would be attractive to gain the maximum therapeutic benefit via delivery of oligonucleotides. Because the claimed invention relates to compositions and methods of delivery of polynucleotides to hybridize to the Bcl-2 gene, *i.e.* in therapeutic applications, a higher uptake of oligonucleotides would be the desirable property. And this desirable property is possessed by the charged lipid example more so than the majority of uncharged lipids, including DOPC. Applicants also note that Tari *et al.* indicates that other lipids tested were easy to handle, but did not exclude charged lipids from having this property (see column 6, lines 53-54). Because the teachings of Tari *et al.* demonstrates desirable properties in both uncharged and charged lipids, this reference does not provide motivation for specifically selecting uncharged lipids from the teachings of charged and uncharged lipids for combining with the other cited references.

Further, Applicants respectfully submit that the Office has not properly considered the previously submitted declaration of Drs. Tari and Lopez-Berestein (attached as Exhibit B) in its evaluation of obviousness or non-obviousness of the claimed invention in light of the cited art. The Office "should consider all rebuttal arguments and evidence presented by applicants" *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), MPEP 2144.08 B. Applicants declaration demonstrates the surprising and unexpected properties of the claimed invention over

the teachings of the cited references, and should be given substantive weight, as described in the MPEP at 2144.08 B:

> However, to be entitled to substantial weight, the applicant should establish a nexus between the rebuttal evidence and the claimed invention, *i.e.* objective evidence of nonobviousness must be attributable to the **claimed invention**. (Emphasis added)

The Action's argument that the "the fact that liposomes comprising 30% negatively or positively charged phosholipids are toxic to cells is inconsequential as Tari *et al* already teaches that neutral lipids are preferred" is an improper dismissal of the evidence presented by the Applicants of the surprising properties of the presently claimed invention.

Further, Applicants contend that all relevant prior art teachings must be considered in evaluation of obviousness (See MPEP 2144.08(II)(A)(4)). Tari *et al.* teaches, at column 2, lines 53-55, "an enhanced **specific** therapeutic effect of the antisense oligonucleotides" (emphasis added) of its invention, which includes both charged and uncharged liposomal constructs. The data presented in this declaration demonstrates that charged liposomes are non-specifically toxic to the tested cell lines. This data is surprising and unexpected because it demonstrates the advantage of the presently claimed invention over the charged and uncharged liposomes taught in Tari *et al.*

Applicants contend in light of the full teachings of the benefits of both neutral and charged liposomes by Tari *et al.*, the evidence of surprising and unexpected advantages associated with the use of antisense Bcl-2 oligonucleotides associated specifically with neutral lipids rebuts any asserted *prima facie* case of obviousness:

> One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected [because] that which

> would have been surprising would not have been obvious. The principle applies most often to predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995).

In light of the forgoing, Applicants respectfully request that this rejection be withdrawn.

F. The Rejection of Claims 1-3, 5-8, 10-31, 33-36, 39, 44, 46, 48-50 and 52-54 Under 35 U.S.C. § 103(a) Over Abukarkr *et al.*, Pocock *et al.* and Cotter *et al.* in view of Tari *et al.* Is Overcome

Claims 1-3, 5-8, 10-31, 33-36, 39, 44, 46, 48-50 and 52-54 are rejected under 35 U.S.C. § 103(a) over Abubakr *et al.* (*Blood* 82 (10 Suppl. 1) 374a, Abstract #1481), Pocock *et al.* (*Blood* 82 (10 Suppl. 1, 200A, Abstract #784) and Cotter *et al.* (*Oncogene*, 9:3049-3055, 1994) as allegedly being obvious in view of Tari *et al.* (U.S. Patent No. 5,417,978).

Applicants respectfully traverse. The claimed invention is not obvious relative to these references, either alone or in combination.

The Action has admitted that Abubakr *et al.*, Pocock *et al.*, and Cotter *et al.*, do not teach "administration of the antisense oligonucleotide as a composition comprising neutral lipids." The Action again relies on the teachings of Tari *et al.* to provide the motivation for combining the teachings of all these references. As with the rejection of the claims described above in section E of this paper, Applicants respectfully submit that the Office, in its arguments for the motivation to combine Tari *et al.* with the other cited references, has incorrectly characterized Tari *et al.* The Action states that one of ordinary skill in the art would be "motivated by the teaching of Tari *et al.* that liposomes comprising dioleolphosphatidylcholine impart improved stability and cellular uptake to the antisense oligonucleotides." Tari *et al.* instead teaches that these properties are common to all liposome constructs, at column 2, lines 49-56. Applicants further find, as previously described in section E of this paper, that Tari *et al.* teaches the benefits

of a charged lipid as having a high oligonucleotide uptake property. Tari *et al.* teaches that a charged liposome contains as much or more oligonucleotides as uncharged lipids, including dioleoylphosphatidylcholine. Thus, the benefits of both charged and uncharged liposomes are taught by Tari *et al.*, and one of skill in the art would not be lead to select only neutral lipids based on the teachings of Tari *et al.*

Applicants respectfully request that this rejection be withdrawn.

G. The Rejection of Claims 4 and 32 Under 35 U.S.C. § 103(a) over Abubakr *et al.*, Pocock *et al.* and Cotter *et al.* in view of Tari *et al.* and further in view of Evan Is Overcome

Claims 4 and 32 are rejected under 35 U.S.C. § 103(a) over Abubakr *et al.* (*Blood* 82 (10 Suppl. 1) 374a, Abstract #1481), Pocock *et al.* (*Blood* 82 (10 Suppl. 1, 200A, Abstract #784) and Cotter *et al.* (*Oncogene*, 9:3049-3055, 1994) as allegedly being obvious in view of Tari *et al.* (U.S. Patent No. 5,417,978) and in further view of Evan (WO 93/20200).

Applicants respectfully traverse. The claimed invention is not obvious relative to these references, either alone or in combination.

Abubakr *et al.*, Pocock *et al.*, Cotter *et al.* and Tari *et al.* do not teach or suggest the claimed invention, as described in section F above. Further, the Action admits that these "references do not teach an antisense oligonucleotide which comprise the sequence of SEQ ID NO:1." The Action's arguments for motivation to combine these references fails. The teachings of Tari *et al.* are to the benefits of both charged and uncharged liposomes or to liposomes in general, rather than neutral liposomes. Tari *et al.* also teaches that a charged lipid possesses a greater uptake of oligonucleotides than the particularly preferred lipid, *i.e.* dioleoyl (C18:1) phosphatidylcholine (see Table 4). Applicants find that Tari *et al.* does not specifically teach or suggest that a charged lipid was not easy to handle (see column 6, lines 53-54). Tari *et al.*

teaches the advantages of both charged and uncharged liposomes without sufficient guidance to a neutral lipid giving the advantageous property of higher oligonucleotide uptake by dioleoyl (C18:1) phosphatidylserine over dioleoyl (C18:1) phosphatidylcholine.

The inclusion of Evan does not make the invention of claims 4 and 32 obvious, as the primary references do not teach or suggest the claimed invention of the independent claims from which these claims depend. The addition of Evan does not provide the motivation to specifically select neutral lipids, as Applicants do not find that this reference teaches neutral lipids.

Applicants respectfully request that this rejection be withdrawn.

REMARKS

The Examiner is invited to contact the undersigned attorney at (512) 418-3000 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Nicole W. Stafford

Nicole W. Stafford
Reg. No. 43,929
Attorney for Applicants

ARNOLD WHITE & DURKEE
P.O. Box 4433
Houston, Texas 77210-4433
(512) 418-3000

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